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Bilateral Choroidal Thicknesses Analysis of Active and Resolved Central Serous Chorioretinopathy

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Abstract

Objectives: This study aimed to examine the choroidal thicknesses (ChT) changes before and after resolution of subretinal fluid in patients with central serous chorioretinopathy (CSR) and in their fellow eyes.

Materials and Methods: Patients with acute CSR were studied and followed until subretinal fluid resolved. Sixty-eight eyes from 34 CSR cases (24 men and 10 women, mean age of 37.34±6.2, range 27-50) were examined. Their ChT was measured using enhanced depth imaging optical coherence tomography (EDI-OCT). Imaging repeated after sub-retinal fluid resolution. ChT changes were analyzed before and after the resolution of subretinal fluid in both eyes.

Results: Mean ChTs in CSR eyes were 387±97 µm, 414±97 µm, and 384±87 µm in 1 mm temporally away from the center, central sub-fovea, and 1 mm nasally away from the center, respectively; and those in the fellow eyes were 283±55 µm, 303±60 µm, and 282±56 µm in the same order. ChT decreased significantly (P≤0.001) to 305±82 µm, 334±86 µm, and 313±76 µm in CSR eyes and to 242±52 µm, 262±55 µm, and 246±48 µm in contralateral eyes in the temporal, central sub-foveal, and nasal sequences after subretinal fluid resolution, respectively. There was a strong correlation between the ChT in active phase and the ChT in resolved phase in both affected and fellow eyes. There was no detectable correlation between central sub-foveal fluid height and sub-foveal choroidal thickness in the affected and fellow eye ($P=0.23$).

Conclusion: Nasal and temporal comparison of the affected and fellow eyes before and after fluid resolution showed that the nasal choroid was thinner than temporal choroid (as the average population) in active phase. In the resolution phase, however, it was the temporal choroid that was thinner than the nasal choroid, and the resolution pattern was not asymmetric.

Keywords: Choroidal thickness, Central serous chorioretinopathy, Fovea, Optical coherence tomography

Introduction

An exudative detachment of the retina in association with a serous detachment of the retinal pigment epithelium is known as central serous chorioretinopathy (CSR). Choroidal layer hyper-permeability and retinal pigment epithelium dysfunction are causes for sub-retinal fluid accumulation around the macular region (1). The higher number of nonvascular smooth muscle cells of the Haller layer of the choroid and their sensitivity to sympathetic tone activation may have a role in CSR pathogenesis (2,3). Previous reports have revealed an increase in the thickness of choroid in the macular region in CSR eyes with optical coherence tomography (OCT) and enhanced depth imaging (EDI) technology (4-8). Furthermore, OCT has shown higher intervascular edema of the choroidal vessels and larger hypo-reflective lumen in CSR eyes than in fellow eyes or control eyes (9). The literature has consistently documented a higher prevalence of CSR in men than in women. It typically occurs in middle-aged men under stress (10, 11). Choroidal thicknesses (ChT) is defined as the distance from the retinal pigmented epithelium (RPE) to the chorio-scleral interface, which can be assessed using EDI-OCT and swept-source OCT. The average thickness of the choroid in the sub-foveal region of healthy adults is between 192 and 354 µm (5,12,13). Studies have indicated that sub-foveal ChT is higher in CSR eyes and uninvolved fellow eyes than in normal control eyes (2,5,14). Some studies have explored the bilateral ChT differences of active form CSR eyes and fellow eyes (8,14), but correlation studies are limited. According to recent studies, normal eyes have thinner choroid in the nasal and inferior parts of the choroid, in the posterior pole (12,13,15,16). Taking into account the results from all recent reports about the possibility of bilateral choroidal involvement in unilateral subretinal fluid accumulation in CSR as well as the limited studies comparing choroidal thickness before and after the resolution, this study aimed to investigate the mechanisms involved in the nasal, central subfoveal, and temporal choroid in eyes with and without subretinal fluid accumulation in the active and resolved CSR phase as well as to identify the pattern of unilateral presentation.

Materials and Methods

A prospective, comparative, observational, and clinical design was adopted in this study. Thirty-four CSR patients admitted to the retina clinic affiliated to Nikookary Eye

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Key Messages

- Though subretinal fluid usually happens in one eye in patients with central serous choroidopathy and choroidal thickness is affected bilaterally.

Hospital of Tabriz, northwest of Iran, from January 2020 to March 2021 were included. All patients were asked about their medical history, current medication, current and previous ophthalmic disease or disorder, and treatments. Exclusion criteria were: previous eye trauma, previous ocular surgery, congenital ocular malformations, recurrent and chronic CSR, absence of subretinal fluid or resolved subretinal fluid signs in imaging, uveitis, diabetes, glaucoma, smoking, significant refractive error (spherical equal to or more than +/-3 diopters), pregnancy, inability to cooperate during OCT, and history of photodynamic therapy, corticosteroid medication, and renal failure. Commercially available OCT, due to low penetration and high backscattering, can visualize the entire choroid only in eyes with high myopia (17-19). The CSR diagnosis was made based on subretinal fluid, absence of drusen, and absence of choroidal neovascular membrane verified by clinical examination, EDI-OCT and fluorescein angiography, and fundus auto-fluorescence. Choroidal thickness was measured using EDI-OCT (SPECTRALIS® HRA OCT, Heidelberg Engineering, Heidelberg, Germany) in the first and last visits. Because of the probable diurnal effect on choroidal thickness (20,21), imaging was performed between 9-11 AM. There was no gold standardized method for measuring choroidal thickness at the time of this study (22). Furthermore, no automated software to measure the choroidal thickness was available at the given time. In this study, the outlines were marked manually by an observer, and the distances were measured using a software (Heidelberg Eye Explorer version 1.6.1.0; Heidelberg Engineering). In addition, 1.5 mm center of the macula was considered as the fovea according to anatomical regions of the macula. Choroidal thickness was measured in central sub-fovea and 1-millimeter lateral sides on the trans-foveolar scan using the manufacturer's software; the segmentation line was set manually to fit the outer border of the retinal pigment epithelium (RPE) – Bruch's membrane complex, and the anterior border of sclera for measuring choroidal thickness. Sub-retinal fluid height in fovea was obtained by manually placing outlines to the superior edge of RPE/Bruch's membrane complex and sub-retinal border. ChTs in active CSR in affected and fellow eyes were compared with ChT after the fluid resolution, and all correlations were evaluated (Figure 1).

All patients were treated with oral propranolol 20 mg on a daily basis for one month and topical dorzolamide drops twice a day for one month. The same individual's fellow eye was used as a control group to eliminate the age effect on choroidal thickness. Patients were followed up monthly until sub-retinal fluid absorption.

Statistical Analysis

Data were analyzed using Statistical Packages for the Social Sciences (SPSS, version 15, Chicago, Illinois, USA). The results were expressed as mean ± standard deviations or percentages, and then the values were compared using two-tailed *t* tests. *P* values of less than 0.05 were considered statistically significant. One-way ANOVA and post hoc multiple comparisons were used to compare the subtracted ChT of temporal, nasal, and central subfoveal after fluid absorption in CSR and contralateral eyes. The correlation analyses of ChT in all macular subfields were performed to compare Pearson correlation between eyes and between two phases.

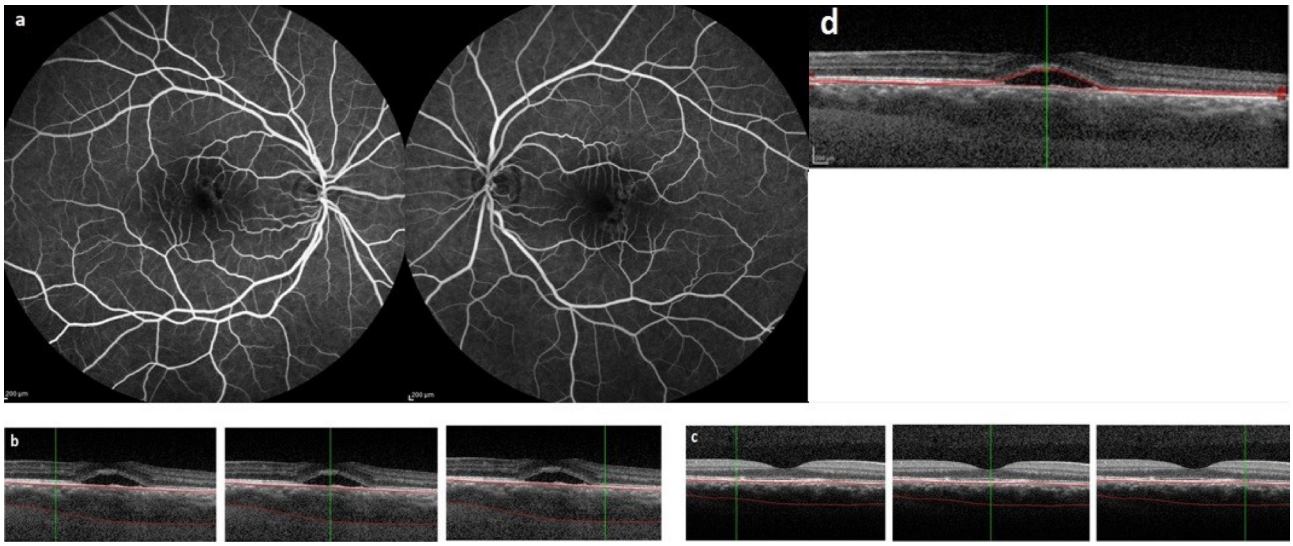

Figure 1. Fluorescein angiography (a) and EDI-OCT Images of CSR Eye (b) and Fellow Eye (c). Sub-foveal ChT and 1 mm temporal and nasal side were measured by manually traced outlines of the choroid and, in a similar fashion, sub-retinal fluid height (d) was obtained by manually adjusted outlines.

Results

ChT of 68 eyes (34 CSR eyes and 34 contralateral control eyes) were obtained and assigned to four groups: before resolution of subretinal fluid in affected eyes, after resolution of subretinal fluid in affected eyes, before resolution of subretinal fluid in fellow eyes, after resolution of subretinal fluid in fellow eyes.

All groups were categorized into three sub-groups of temporal, sub-foveal, and nasal in order for analyzing choroidal thickness changes (Table 1).

There was no detectable correlation between sub-foveal fluid height and sub-foveal choroidal thickness before and after subretinal fluid resolution ($P = 0.23$), but a significant correlation was detected in the active and resolved CSR phase in affected and fellow eyes ChT (Tables 2 and 3). One-way ANOVA and pos hoc tests multiple comparison results revealed that there was no statistically significant difference between active and resolution phases in fellow eyes (Table 4).

Discussion

There is a wide normal range of sub-foveal choroidal thickness in the population. Average ChT depends on age, race and significant refractive error, and it decreases with age (16,23,24). Some medical conditions, such as smoking (25) and diabetes mellitus (13,26), as well as ocular pathologies like glaucoma (27,28) and myopia (15,29), can influence ChT. Choroidal hyperpermeability, dilated choroidal vessels, and focal or diffuse increase in choroidal thickness are features of the pachychoroid spectrum, including uncomplicated pachychoroid , pachychoroid pigment epitheliopathy (PPE), CSR, pachychoroid neovasculopathy, and polypoidal choroidal vasculopathy (30-32). Warrow et al defined PPE as a forme fruste of CSR, and then several studies highlighted that PPE is typical in fellow eyes of patients with CSR and, therefore, they define PPE as choroidal thickness more >300 µm in any location or an extrafoveal focus exceeding the choroidal thickness of fovea by at least 50 µm and without resolved CSR signs (i.e., distinct interruption of the interdigitation zone, ellipsoid zone, external limiting membrane and, distinct thinning of inner retinal layers at the lesion area) (30,33-37). For the first time, Margolis and Spaide determined choroidal thickness in normal eyes sub-foveally to be 287 ± 76 µm by adopting EDI-OCT technique, varying topographically within the posterior pole area (23). Further investigations have demonstrated that the subfoveal ChT in healthy adults ranges from

Table 1. Demographical Information and Imaging data

Variable	N/mean ± SD	%	Range
Demographic Data			
Age (y)	37.34±6.2	-	27-50
Gender			
Male	24	70.6	-
Female	10	29.4	-
Eye			
Right	19	55.9	-
Left	15	44.1	-
Resolution period (mon)	4.7 ±3.3	-	2-12
Sub-foveal fluid height (µm)	259±104	-	85-491

	Imaging Data					
	Affected Eye (Mean ± SE)			**Fellow Eye (Mean ± SE)**		
	Before Subretinal Fluid Resolution	**After Subretinal Fluid Resolution**	***P***	**Before Subretinal Fluid Resolution**	**After Subretinal Fluid Resolution**	***P***
Choroidal thickness(µm)						
Temporal	387±97	305±82	<0.001	283±55	242±52	<0.001
Central sub-foveal	414±97	334±86	<0.001	303±60	262±55	<0.001
Nasal	384±87	313±76	<0.001	282±56	246±48	<0.001

ChT: Choroidal Thickness, CSR: Central Serous Chorioretinopathy, SD: Standard Deviation, SE: Standard Error

Table 2. Correlation of Choroidal Thicknesses in Both Eyes in the Same Phase

Thickness	**Pearson Correlation**					
	1mm Temporal ChT		**Central Sub-foveal ChT**		**1mm Nasal ChT**	
	r	***P***	**r**	***P***	**r**	***P***
Active CSR phase in affected and fellow eye	0.65	<0.001	0.65	<0.001	0.55	0.001
Resolved CSR phase in affected and fellow eye	0.68	<0.001	0.67	<0.001	0.655	<0.001

ChT: choroidal thickness, CSR: central serous chorioretinopathy.
Correlation is significant at the 0.01. (Correlation coefficient: 1 exact, 1-0.7 perfect vs very strong, 0.7-0.5 strong, 0.5-0.3 moderate, 0.3-0.1 weak, 0.1-0 little vs very weak).

Table 3. Correlation of Choroidal Thickness in Active and Resolved Phase in the Same Eye

Thickness	Pearson Correlation					
	1 mm Temporal ChT		Central Sub-foveal ChT		1 mm Nasal ChT	
	r	*P*	*r*	*P*	*r*	*P*
Active and resolved CSR phase in affected eye	0.83	<0.001	0.83	<0.001	0.80	<0.001
Active and resolved CSR phase in fellow eye	0.86	<0.001	0.87	<0.001	0.82	<0.001

ChT: choroidal thickness, CSR: central serous chorioretinopathy.
Correlation is significant at the 0.01. (Correlation coefficient: 1 exact, 1-0.7 perfect vs very strong, 0.7-0.5 strong, 0.5-0.3 moderate, 0.3-0.1 weak, 0.1-0 little vs very weak).

Table 4. One-way ANOVA and Pos Hoc Tests Multiple Comparison Results Between Active and Resolution Phase Difference in CSR Eyes

Macular Subfields	N	Mean Difference Between Active and Resolved	Macular Subfields	Mean Difference Between Subfields Difference	*P*
Temporal	34	81.20	Nasal	9.47	0.74
			Central subfoveal	1.08	0.99
Central sub foveal	34	80.11	Temporal	-1.08	0.99
			Nasal	8.38	0.79
Nasal	34	71.73	Temporal	-9.47	0.74
			Central subfoveal	-8.38	0.79
P		0.72			

P value is significant at the 0.05 level (two-tailed).

297.8 ± 82.2 by spectral-domain OCT imaging to 341 ± 95 μm by three-dimensional 1060-nm OCT (5, 12, 13). According to the EDI-OCT imaging results (12,14), active CSR phase ChT was out of normal limit. ChT is affected by many factors. It was more useful to compare bilateral ChT patterns before and after subretinal fluid resolution to explain the acute CSR phase in the choroid. Yang et al reported higher sub-foveal ChT for the CSR eyes (455 ± 73 μm) than for contralateral unaffected eyes (387 ± 94 μm), and higher ChT for contralateral unaffected eyes than for the control group (289 ± 71 μm) (9). Similar results were reported in previous investigations on an increased choroidal thickness in eyes with CSR compared to the contralateral eyes of the same patients (6-8,23). Maruko et al showed the choroid was thicker in the fellow eyes. However, the choroid was thicker in the fellow eyes with choroidal vascular hyperpermeability on ICGA. The choroid was not thicker in the fellow eyes without hyperpermeability, but CSR may have become bilateral during follow-up. Bilateral ChT increment supports a presumptive systemic etiology for the disease. Choroidal thickening is seen as a response to intraocular and extraocular pressure since the choroidal vasculature can easily leak or expand and contract (38).

Aggravation of CSR by endogenous or exogenous glucocorticoids was proven in many studies (39-43). Zhao et al showed the glucocorticoids tend to bind mineralocorticoid receptors in rat choroid led to choroidal thickening (42). Singh et al used mineralocorticoid receptor antagonist (oral eplerenone) for managing the chronic CSR, and found that diameter and height of subretinal fluid and central sub-foveal ChT in SD-OCT decreased over time (44). Brandl et al compared CSR choroidal changes in fellow eyes and healthy control group. Choroidal thickness measurements were performed in 5 points, sub-foveal, 0.5 and 1 mm nasal and temporal from the center; after three months, the choroidal thickness of the affected eyes showed a highly significant decrease but did not reach normal ranges. Changes were also observed in the fellow eyes, but they were not statistically significant (45). In our study, the CSR patients were followed until sub-retinal fluid resolution (range 2 to 12 months), and it was confirmed that ChT in CSR eyes and fellow eyes decreased significantly after fluid resolution. A very strong correlation ($r = 0.5$-0.7) was discovered in temporal, sub-foveal, and nasal thickness data of both eyes in the same phase, and a perfect correlation ($r = 0.7$-0.99) was observed in the active and resolved phases in the same eye. In the posterior pole of the normal population, the nasal and inferior parts of the choroid are thinner than those of the temporal. These findings may be responsible for the vascular watershed zone and the embryonic location of optic fissure closure (12,13,15,16). Nasal and temporal comparison of each eye before and after fluid resolution showed that the nasal choroid was thinner than the temporal (as average population) in the active phase, but in the resolution phase, it was the temporal choroid that was thinner than the nasal ($P < 0.001$). Subtraction values in the same points before and after fluid resolution were not statistically significant ($P > 0.05$).

Limitations of Study

Our study faced some limitations. First, placing outlines manually was an exhausting practice and may have reduced the accuracy of the results due to the lack of an

effective automated grading algorithm, which can also introduce measurement bias. As documented by Kim et al, this was an ongoing limitation of all studies on choroidal thickness measurements and OCT at the time of our study (39). Second, it was not possible to control some systemic factors (e.g., hydration status). Third, the results may have been more reliable if the measurements were out of the fovea and were performed in the vertical line to evaluate the gravitational effect in the upright position of the imaging.

Conclusions

In sum, it was found that CSR was the bilaterally involved in choroidal process, and the resolution phase occurred bilaterally as well. Moreover, the resolution pattern was asymmetric nasal. The temporal comparison of each eye before and after fluid resolution showed that the nasal choroid was thinner than temporal as normal population in the active phase, but in the resolution phase, it was the temporal choroid that was thinner than the nasal.

Authors' Contribution

BKG collected the data, Conceived and designed the analysis, wrote the paper. AAEM collected the data, contributed data or analysis tools, performed the analysis. AQ collected the data, contributed data or analysis tools, performed the analysis. MRN conceived and designed the analysis, performed the analysis, wrote the paper.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

The study was approved by the medical ethics committee of Tabriz University of Medical Sciences, and was performed in accordance with the Declaration of Helsinki (Ethics No. IR.TBZMED.REC.1399.164).

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